REMARKS

Claim 61 is pending in the subject application. By this Amendment, applicants have amended claim 61. No new matter is introduced by the amendments to claim 61 which are fully supported in the specification at, *inter alia*, page 1, line 19 to page 2, line 3; page 2, lines 28-34; page 7, lines 3-30; Figure 1; page 26, lines 3-18; page 31, lines 15-28; page 34, lines 12-37; page 35, Table 2a; page 36, lines 17-39; and page 39, line 39 to page 41, line 8. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claim 61 will still be pending and under examination.

The Claimed Invention

The subject invention is directed to a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1, which method comprises contacting the CD4+ cell with an agent (a) capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell; (b) capable of blocking fusion of HIV-1_{JR-FL} with a PM-1 cell; and (c) not capable of blocking fusion of HIV-1_{BRU} with such PM-1 cell, in an amount and under conditions such that the fusion of the macrophage-tropic HIV-1 or a macrophage-tropic HIV-1-infected cell to the CD4+ cell is inhibited, so as to thereby inhibit infection of the CD4+ cell by the macrophage-tropic HIV-1.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejected claim 61 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981); *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90. (C.C.P.A. 1976)). The Examiner stated that the claim has been amended to introduce a new limitation vis-a-vis the binding specificity of the non-peptidyl agent. The Examiner further stated that the claim now specifies that the agent of interest is capable of binding to the CCR5 chemokine receptor, but not the CXCR4 chemokine receptor. The Examiner also stated that perusal of the disclosure failed to provide support for the claimed limitation.

In response, applicants respectfully traverse this rejection.

Without conceding the correctness of the Examiner's position, applicants note that claim 61, as amended, does not recite that the agent of interest is capable of binding to the CCR5 chemokine receptor but not the CXCR4 chemokine receptor. Instead, the agent must be capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell and blocking fusion of HIV-1_{JR-FL} with a PM-1 cell, but not capable of blocking fusion of HIV-1_{BRU} with such PM-1 cell. Support for an agent with these properties is provided in the specification at, *inter alia*, page 34, lines 12-37 and page 35, Table 2a, and numerous examples of chemokine (see, *inter alia*, page 7, lines 3-12; Figure 1; page 34, lines 33-37 and page 35, Table 2a) and non-chemokine agents (see, *inter alia*, page 13, line 33 to page 15, line 3; and page 26, line 29 to page 28, line 1) are provided in the specification.

Applicants therefore respectfully submit that the above rejection should be withdrawn.

Written Description

The Examiner also rejected claim 61 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981); *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90. (C.C.P.A. 1976); *In re Rochester*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004)). The Examiner stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (citing, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935F.2d at 1563, 19 U.S.P.Q.2d at 1116). The Examiner also stated that the issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of non-peptidyl agents that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. The Examiner further stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)).

In addition, the Examiner stated that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making, coupled with its function, and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. The Examiner stated that a biomolecule sequence, described only by functional characteristic without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest (citing *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993); *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995)).

The Examiner stated that a lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process (citing, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995)). The Examiner further stated that the court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

The Examiner also stated that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner further stated that an applicant may also

show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete, or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The Examiner additionally stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight.

The Examiner stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner further stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. The Examiner also stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement (citing *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998); *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984)). The Examiner noted that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between

structure and function, and the method of making the claimed invention.

The Examiner stated that the claim of the instant application is broadly directed toward any non-peptidyl agent that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The Examiner also stated that the disclosure provides an *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. The Examiner stated that, however, the disclosure fails to provide any structural guidance pertaining to suitable non-peptidyl compounds that can reasonably be expected to function in the claimed methodology. The Examiner also stated that the only non-peptidyl compound described in the specification is specific for CXCR4, not CCR5. The Examiner further stated that the disclosure fails to identify suitable chemical compounds with the desired activity. The Examiner also stated that the disclosure fails to provide any guidance pertaining to the three-dimensional configuration of the CCR5 receptor. The Examiner stated that the skilled artisan thus cannot employ a rational drug-screening strategy. The Examiner also stated that applicants have basically provided a generic screening method and invited the skilled artisan to figure out which non-peptidyl compounds may be reasonably expected to function in the recited manner. The Examiner concluded that this clearly fails to meet the requirements set forth under this statute.

In response, applicants respectfully traverse this "written description" rejection.

Without conceding the correctness of the Examiner's position,

applicants note that claim 61, as amended, does not recite that the agent of interest is capable of binding to the CCR5 chemokine receptor but not the CXCR4 chemokine receptor. Instead, the claim requires that the agent be capable of binding to a CCR5 chemokine receptor on the surface of a CD4+ cell and blocking fusion of HIV-1_{JR-FL} with a PM-1 cell, but not capable of blocking fusion of HIV-1_{BRU} with such PM-1 cell. Further, as noted above, the specification provides numerous examples of suitable chemical compounds with the desired activity, including chemokine (see, *inter alia*, page 7, lines 3-12; Figure 1; page 34, lines 33-37 and page 35, Table 2a) and non-chemokine agents (see, *inter alia*, page 13, line 33 to page 15, line 3; and page 26, line 29 to page 28, line 1).

Applicants also disagree with the Examiner's assertion that the skilled artisan thus cannot employ a rational drug-screening strategy. On the contrary, applicants maintain that the specification provides a rational drug-screening strategy based on the resonance energy transfer (RET) assay (see, *inter alia*, page 9, line 22 to page 20, line 1; page 20, lines 12-20; page 26, lines 32-34; page 35, line 9 to page 36, line 4. Applicants note that the Examiner appears to be underestimating the power, flexibility and efficacy of the RET assay in identifying agents that inhibit HIV-1 infection of CD4+ cells, even without any prior knowledge of the chemical structures of these agents, and without undue experimentation. In this regard, applicants note that Dr. Tatjana Dragic has previously attested to the efficacy of the RET assay in so identifying inhibitors of HIV-1 infection in her two Declarations filed in the subject application on March 31, 2002 (Dragic Declaration I) and August 26, 2003 (Dragic Declaration II). Applicants respectfully submit that the

Examiner has impermissibly ignored the evidence presented in Dr. Dragic's two Declarations and substituted his own personal opinions therefor.

In view of the above remarks and arguments, applicants maintain that claim 61, as amended, satisfies the written description requirements of 35 U.S.C. §112, first paragraph.

Enablement

The Examiner also rejected claim 61 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that the claim is broadly directed toward a method for inhibiting HIV-1 infection of $CD4^+$ cells through the administration of a non-peptidyl inhibitory agent that is capable of binding to the CCR5 chemokine coreceptor.

The Examiner stated that as previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986)). The Examiner also stated that the courts concluded that several factual inquiries should be considered when making such assessments, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of

the art and the breadth of the claims (citing *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965)). The Examiner further stated that the disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The Examiner stated that the disclosure fails to provide any guidance pertaining to the structural requirements of any given non-peptidyl inhibitor. The Examiner also stated that the disclosure fails to teach which chemical structures are critical for binding to any given chemokine coreceptor and which structures are critical for the antiviral activity. The Examiner further stated that the disclosure fails to identify any parent compounds, or derivatives thereof, that can reasonably be expected to function in the desired manner. The Examiner also stated that the skilled artisan has thus been extended an undue invitation to further experimentation to try to identify putative antiviral agents and determine their structures.

2) The Examiner stated that the disclosure fails to provide sufficient guidance pertaining to the three-dimensional structure of CCR5 or the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral binding interactions. The Examiner also stated that in order to rationally design a putative therapeutic, the skilled artisan would need a knowledge of those portions of CCR5 or CXCR4 that should be targets of any given antiviral. The Examiner further stated that, however, the specification is silent pertaining to this concern and fails to identify any critical regions of the chemokine coreceptors that should be the targets of antiviral

development.

3) The Examiner stated that the disclosure fails to provide any working embodiments that meet the claimed limitations. The Examiner noted that while the disclosure describes the identification of a putative antiviral agent (e.g., JM3100), this compound is, nevertheless, a bycyclam agent that is directed toward CXCR4, not CCR5. The Examiner also stated that there are no other examples involving non-peptidyl agents provided in the disclosure.

4) The Examiner stated that the claims are of excessive breadth and encompass any given putative antiviral agent without providing any meaningful structural limitations concerning that agent. The Examiner also stated that the disclosure simply fails to support such breadth in the claim language.

5) The Examiner stated that the prior art describes a number of concerns pertaining to the development of antivirals, particularly fusion inhibitors. The Examiner also stated that, first, it is well-known that the chemokine family includes a large number of proteins that share limited genetic relatedness (~20%; citing Proudfoot et al., 1999; Proudfoot et al., 2000). The Examiner further stated that it thus appears unlikely that any given inhibitor will have a broad range of activity, particularly in the absence of the identification of any critical molecular determinants that are shared by all members of the family. The Examiner additionally stated that, second, even if a putative antiviral compound was identified, there are a number of important immunological or

> therapeutic concerns that need to be considered (citing Berger et al., 1999). The Examiner asked whether, for instance, the loss of normal chemokine receptor function of a specific coreceptor would be tolerated and accepted in the host. The Examiner also asked whether the impairment of CCR5 coreceptor usage would accelerate disease progression by enhancing the selection for CXCR4 coreceptor usage. The Examiner asked whether multiple members of the coreceptor repertoire needed to be blocked in order to achieve a therapeutic effect. The Examiner stated that the disclosure is silent pertaining to these concerns.

In response, applicants respectfully traverse this "enablement" rejection. Applicants note that 35 U.S.C. §112, first paragraph, requires that:

> "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, ..." (emphasis added)

Applicants maintain that the method of claim 61, as amended, is fully enabled by the specification as filed. Regarding the Examiner's statement that the disclosure fails to provide any guidance pertaining to the structural requirements of any given non-peptidyl inhibitor, applicants note that claim 61, as amended, is directed to a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1, which method comprises contacting the CD4+ cell with an agent capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell and blocking fusion of HIV-1_{JR-FL} with a PM-1 cell, but not capable of blocking fusion of HIV-1_{BRU} with such PM-1

cell. Applicants note that, more that the specification providing guidance pertaining to the structural requirements of suitable agents, it provides numerous examples of suitable chemical compounds with the desired activity, including chemokine (see, *inter alia*, page 7, lines 3-12; Figure 1; page 34, lines 33-37 and page 35, Table 2a) and non-chemokine agents (see, *inter alia*, page 13, line 33 to page 15, line 3; and page 26, line 29 to page 28, line 1).

Regarding the Examiner's statement that the disclosure fails to provide any guidance pertaining to the three-dimensional structures of CCR5 or the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral binding interactions, applicants assert that knowledge of these structures not required for successfully using the RET assay, without undue experimentation, to practice the claimed method of the invention. In support of this assertion, applicants respectfully direct the Examiner's attention to Dragic Declaration II, paragraph 12, and Dragic Declaration I, paragraphs 15-17.

Applicants emphasize that in order to overcome the evidentiary weight to which the statements in Dr. Dragic's Declarations are entitled, the Examiner may not rely, as he continues to do, simply on his own unsupported opinion of what scope of disclosure is required to enable one of ordinary skill in this art to practice the invention. Instead, the Examiner is required to point to some tangible source, i.e., a patent, treatise, journal article or some other disclosure, to "disprove" the contentions set forth in the declaration and this he has so far failed to do.

Regarding the Examiner's statements that the disclosure fails to provide any working embodiments that meet the claimed limitations, and that the claims are of excessive breadth and encompass any given putative antiviral agent without providing any meaningful structural limitations concerning that agent, applicants maintain that these assertions do not apply to claim 61, as amended. Applicants note again that the specification provides numerous examples of both chemokine (see, *inter alia*, page 7, lines 3-12; Figure 1; page 34, lines 33-37 and page 35, Table 2a) and non-chemokine agents (see, *inter alia*, page 13, line 33 to page 15, line 3; and page 26, line 29 to page 28, line 1) that meet the claim limitations.

In item no. 5 above, the Examiner raised questions relating to immunological, therapeutic and clinical concerns and possible harmful side effects that he believes need to be considered, and stated that the disclosure is silent pertaining to these concerns.

In response, applicants respectfully submit that these questions about clinical efficacy are irrelevant since they fall within the province of the Food and Drug Administration (FDA) but outside of patent law. In this regard, applicants respectfully direct the Examiner's attention to *In Re Brana* (51 F.3d 1560, 1567, 34 U.S.P.Q.2d 1436, 1442, Fed. Cir. 1995, *per* Plager, Circuit Judge):

> The Commissioner counters that such in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means in vivo testing in humans, and therefore not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the

> requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.") (emphasis added).

Applicants therefore maintain that questions as to whether, for example, the loss of normal chemokine receptor function of the CCR5 receptor would be tolerated in a subject, or whether the impairment of CCR5 coreceptor usage would accelerate disease progression by enhancing the selection for CXCR4 coreceptor usage, or other similar safety considerations, fall outside the requirements for patentability.

The Examiner also stated that it has been well-established that the development of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure (citing Oberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997). The Examiner further stated that this is due to a number of considerations such as a failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The Examiner also stated that the difficulties associated with developing

efficacious anti-HIV-1 agents are best summarized by Gait and Karn (1995) who state (citing the Conclusions at p.37):

> There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivities for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The Examiner stated that the disclosure fails to provide any guidance pertaining to these caveats. The Examiner asserted that, accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

In response, applicants contend that the Examiner's continued reliance on references such as Gait and Karn (1995), as summarizing the prior art, is without merit. Applicants note that Gait and Karn (1995) relates to protease inhibitors as antiviral drugs. Applicants note, further, that as previously discussed in their Amendments filed August 27, 2003 (pages 31-32) and April 2, 2002 (page 9), the teaching of Gait and Karn (1995) is irrelevant to the present invention which does not pertain to or involve a protease inhibitor. Thus, difficulties encountered in the development of a protease inhibitor as a clinical therapeutic are not relevant to the

use of an agent that binds to a CCR5 chemokine receptor on CD4+ cells and thereby inhibits fusion with HIV-1 or an HIV-1-infected cell. The Examiner appears to be suggesting that no therapeutic for inhibiting HIV-1 infection can be developed because, in part, Gait and Karn (1995) teaches that the development of a protease inhibitor therapeutic has proven to be challenging. Applicants respectfully submit that this viewpoint is not tenable.

The Examiner stated that applicants provide a detailed traversal and submit that the invention is fully enabled. The Examiner also stated that it was argued that the disclosure provides a RET assay that can be utilized to screen for suitable compounds. The Examiner further stated that reference was made to a second Declaration by Dr. Dragic. The Examiner stated that Dr. Dragic also asserted that the specification provides a generic RET screening method which can be utilized to identify compounds with the desired properties. However, the Examiner additionally stated that this Declaration did not provide any data demonstrating that applicants had identified such compounds at the time of filing. The Examiner noted that Exhibits were also provided in support but stated that the majority of these Exhibits were published well after the filing data of the claims.

The Examiner reminded applicants that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (citing M.P.E.P. §2164.05 (a)). The Examiner stated that publications dated after the filing date and providing information publicly first disclosed after the filing date generally cannot be used to show what was known

at the time of filing (citing *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976); *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976)). The Examiner stated that the observation that others have come up with a small number of compounds well after the filing date of the instant application would thus not lead the skilled artisan to conclude that the invention was enabled at the time of filing.

In response, and without conceding the correctness of the Examiner's position, applicants note again that the method of claim 61, as amended, requires an agent that is capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell and blocking fusion of HIV-1_{JR-FL} with a PM-1 cell, but not capable of blocking fusion of HIV-1_{BRU} with such PM-1 cell. Applicants note also that the specification as filed provides numerous examples of agents with the specified activities. Applicants maintain that since these agents were identified as of the filing date, the Examiner's rejection based on the alleged unacceptability of post-filing data is moot.

Applicants therefore maintain that the specification as filed satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, with regard to pending claim 61, as amended.

Conclusion

In view of the remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the claim rejections set forth in the April 20, 2004 Office Action, and earnestly solicit allowance of all claims pending in the subject application.